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10/577,973	06/26/2006	Barbara Ensoli	50318/013001	3019

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EXAMINER	
KASSA, TIGABU	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/577,973	ENSOLI ET AL.	
	Examiner	Art Unit	
	TIGABU KASSA	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *9 and 16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed November 25, 2009.

Claims 1-20 are currently pending. Claims 1-8 and 10-15 are under consideration in the instant office action. Claims 9 and 16-20 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claims. Claims 21-23 are cancelled. Applicant's amendment for example in instant claim 7 has necessitated a new ground of rejection. Accordingly, this Action is FINAL.

Information Disclosure Statement

The information disclosure statement (IDSs) submitted on 12/19/07 is noted and the submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the references. The examiner also considered the reference Arya et al. However, the examiner did not consider CZ 223295 and DE 10118852 because the two references as filed fail to comply with 37 CFR 1.98(a)(3) because the information disclosure statement with regard to these references does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, **of each patent listed that is not in the English language**. It has been placed in the application file, but the information referred to therein has not been considered.

Withdrawn rejections

Applicant's amendments and arguments filed on 11/25/09 are acknowledged and have been fully considered. The rejections applied in the previous office action under 35 U.S.C. 102(b) are hereby withdrawn as a result of applicants claim amendments.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Instant claim 1 is amended to recite a limitation wherein the said "nanoparticles having a number average particle diameter measured by scanning electron microscopy of 500 nm or less". Applicants' original specification does not have a written support for particle size diameter of 500 nm or less. Applicants' specification discloses that "The nanoparticles of the invention generally have a number-average particle diameter measured by scanning electron microscopy of less than 1100 nm, preferably 50 to 1000 nm, more preferably 50 to 500 nm, e.g. 50 to 300 nm." Based on this disclosure the lower end of the range is 50 nm. However, instant claim 1 recites 500 nm or less which includes particle sizes less than 50 nm.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness

Claim 1-3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laus et al. (Journal of Controlled Release 2001, 72, 225-309)) as evidenced by Specification and test methods for EUDRAGIT® L 100-55, Degussa.

Applicant Claims

Applicants claim nanoparticles comprising a core of a water insoluble polymer or copolymer and a shell of a hydrophilic polymer or copolymer comprised of the specified monomers. Further limitations specify the monomers used to form the core polymers, wherein the number average particle diameter is 500 nm or less.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Laus et al. teach **microspheres with hydrophilic and protein-friendly surfaces as protein delivery systems prepared by dispersion polymerization** (page 280, title). Laus et al. also teach **dispersion polymerization is a process which generates latex microspheres in the 0.5 to 20 microns diameter range** (page 280, introduction). The examiner reminds applicants that the particle size diameter taught by Laus et al. is also an evidence that dispersion polymerization can also result in microspheres having particle diameter of 500 nm. The cores are made of **either polystyrene or methylmethacrylate** (page 280, introduction). The methylmethacrylate microspheres are coated with a steric stabilizer of Eudragit L100/55. The Eudragit polymer is a methlacrylic acid ethylmethacrylate as evidenced by Specification and Test methods for Eudragit L100-55 (section 2, Chemical structure), Degussa.

Ascertainment of the Difference between Scope the Prior Art and the Claims (MPEP §2141.012)

The general teaching by Laus et al. for the particle size diameter overlaps with the instantly claimed range rendering it obvious. However, Laus et al. do not teach the particle diameter in anticipating range.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary in the art at the time the invention was made to produce the invention in the particle size as recited, because Laus et al. teach similar composition in overlapping particle size range. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Similarly, a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Moreover, based on (see MPEP 2144.05 *In re Aller*, 220 F. 2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)) "differences in concentration which is in the instant case the particle size diameter will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or particle size diameter is critical. It is not inventive to discover the optimum or workable ranges by routine experimentation." The skilled artisan would have been motivated to select a particle size range which is suitable for administration to animals or humans since the work of Laus et al. is presented in an article entitled Novel Therapeutic Delivery Systems which is found in the Journal of Controlled Release. The skilled artisan would have a reasonable expectation of success at optimizing the particle sizes of the nanoparticles since such routine optimization is within the purview of the skilled artisan. The examiner notes that instant claim 1 also incorporates a product-by-process language wherein the product being obtainable by emulsion polymerization. The examiner takes the position that the product of the instant invention is obvious from the

product of the prior art because "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). The skilled artisan would have had a reasonable expectation of success in following the teachings of Laus et al. to produce the instant invention because Laus et al. teach substantially similar particles as set forth above.

Applicants have not demonstrated how their product is patentably distinct from the cited prior arts nor do the claims as currently written distinguish the instant invention over the prior arts. In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicant's arguments filed 11/25/09 have been fully considered but they are not persuasive. The examiner rebuts applicants arguments filed on 11/25/09 to the extent they apply to the instantly applied rejection as set forth above. *Applicants argue that although Laus states that, in general, dispersion polymerization is a process that generates latex microspheres in the 0.5 to 20 micron diameter range, there is no*

disclosure or suggestion in Laus that dispersion polymerization using the conditions, materials, and methods specifically described by Laus achieves or is capable of achieving the lower limit of 0.5 micron diameter. The examiner respectfully disagrees with applicants' assertion because Laus et al. even if it does not teach in a specific embodiment the particle size diameter range Laus et al. clearly acknowledges that it is known in the art that the dispersion polymerization technique can result in particles with diameters of 500 nm-20 microns. For Laus et al. to render obvious the instantly claimed invention it does not have to teach in a single embodiment the particle size diameter so long as one of ordinary skill in the art would infer from the teaching of Laus et al. it is possible to make particles with diameter of 500 nm using the dispersion polymerization technique. *Applicants also argue that "The microspheres of Laus are produced using a different process from the process by which the nanospheres of the instant application are produced. As explained above, Laus uses a dispersion polymerization process that features the polymerization of a monomer dissolved in an organic diluent in the presence of a polymeric stabilizer. Laus does not enable the production of particles less than 650 nm in diameter. The instant application describes the synthesis of polymeric nanoparticles by emulsion polymerization with diameters 0.50 microns or lower."* The examiner respectfully disagrees with these assertions because the product of the instant invention is obvious from the product of the prior art because "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product

was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Applicants also argue that the process used by Laus et al. is not enabled for making 500nm particles. The examiner respectfully disagrees because applicants failed to provide any solid reasoning or evidence to show that the process of Laus et al. cannot make the entire size range taught by the reference. As it is clearly described above the dispersion polymerization method is capable of making particles with diameter of 500 nm-20 microns, absence of evidence to the contrary.

Applicants have not demonstrated how their product is patentably distinct from the cited prior arts nor do the claims as currently written distinguish the instant invention over the prior arts. In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laus et al. (Journal of Controlled Release 2001, 72, 225-309) in view of Bayer (US 2003/0087436).

Applicant Claims

The claimed subject matters of instant claim 1 are set forth above. Instant claim 7 recites nanoparticles according to instant claim 1 which have a number average particle diameter of from 50 to 300 nm.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Laus et al. are set forth above.

Ascertainment of the Difference between Scope the Prior Art and the Claims (MPEP §2141.012)

Laus et al. do not teach the particle size of from 50 to 300 nm. This deficiency is cured by the teachings of Bayer.

Bayer teaches **a process for producing biologically active polymer nanoparticle-nucleic acid conjugates by polymerizing vinyl monomer with low-water solubility in an aqueous solution, then reacting the resulting polymer suspensions with the nucleic acids** (abstract and claim 1). Bayer teaches **in example 3 polymer suspension having particles with an average particle diameter of 150 to 200 nm that have a considerably monodisperse size distribution** (paragraph 0040). The polymeric particles have **a particle size of preferably 10 to 1000 nm** (paragraph 0021 and claim 6).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious to one of ordinary in the art at the time the invention was made to modify the teachings of Laus et al. via making particles with particle sizes as recited in instant claim, because Bayer teaches biologically active polymer nanoparticle-nucleic acid conjugates by polymerizing vinyl monomer with low-

water solubility in an aqueous solution with an average particle diameter of 150 to 200 nm that have a considerably monodisperse size distribution (paragraph 0040). Furthermore, Bayer teaches the polymeric particles have a particle size of preferably 10 to 1000 nm (paragraph 0021 and claim 6). The skilled artisan would have been motivated to modify the particle size diameter of 50 to 300 nm because Bayer teaches that by varying the size, type and surface charge of the polymeric nano-particle parent substance by selection of the effective nucleic acid components and their derivation as well as by modification of the surface by means of basic peptides or polyethylenimine, the polymeric nanoparticle-nucleic acid systems can be adjusted to the respective requirements of the biological test systems (paragraph 0031). In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Moreover, based on (see MPEP 2144.05 *In re Aller*, 220 F. 2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)) "differences in concentration or in particle size diameter will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such particle size diameter is critical. It is not inventive to discover the optimum or workable ranges by routine experimentation." The skilled artisan would have had a reasonable expectation of success in combining the teachings of Laus et al. and Bayer because both references teach nanoparticle based delivery of macromolecules.

In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have

been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Maintained Rejections

Claims 1 and 4 are rejected 35 U.S.C. 103(a) as being unpatentable over Laus et al. (Journal of Controlled Release 2001, 72, 225-309) in view of Schacht et al. (US Patent 6312727).

Applicant Claims

The limitations of instant claim 1 are set forth above. Instant claims 4 further specify the monomers used to form the nanoparticles.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Laus et al. are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Laus et al. do not teach the specific monomers recited in instant claim 4. This deficiency is cured by Schacht et al.

Schacht et al. teach polymer-based carrier vehicles for the delivery of nucleic acid material to target cells (abstract). The outer protective shield of the delivery system may be based on **acrylic or methacrylic monomers having reactive amino or alkyl amino functional groups** (abstract and column 19, lines 19-21). Specifically such monomers

may include **acrylic or methacrylic monomers terminating in an alkyl amino group** (column 19, lines 35-41).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary in the art at the time the invention was made to select a monomer which is a derivative of a methacrylic acid since Laus et al. already teach the use of methacrylic acid monomers for coating the nanoparticles. The skilled artisan would have been motivated to use polymers with reactive alkyl amino functional groups (which would include those monomers found in instant claim 4) since they are taught by Schacht et al. as being suitable for bonding and forming a protective coating or shield (abstract and column 19, lines 22-25). The skilled artisan would have a reasonable expectation of success at combining the prior art teachings since the Laus et al. and Schacht et al. both use similar polymers for coating vehicles or particles for use with biological macromolecules.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicants' arguments filed 11/25/09 have been fully considered but they are not persuasive. *Applicants argue that since claim 4 incorporates the features of claim 1 and claim 1 is not obvious as per the arguments set forth above instant claim 4 is not also obvious.* The limitations of instant claim 1 are clearly rendered obvious and applicants' arguments regarding instant claim 1 are rebutted as set forth above. Since those rebuttal

arguments also apply in this section of the rejection the examiner incorporates the rebuttal arguments by reference in this section too. *Applicants also assert that Schacht does not teach nanoparticles with an average diameter of 500 nm or less. Based on this deficiency alone, this rejection may be withdrawn. Moreover, the skilled artisan would not have been motivated to combine the teachings of Schacht and Laus, as the particles taught by each reference are based on incompatible technologies.* The examiner respectfully disagrees with applicants' assertions because applicants are resorting to attacking the references individually while the rejection is based on the combination teachings of Laus et al. and Schacht et al. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Additionally, for Schact et al. to be a proper prior art it does not have to teach nanoparticles of 500 nm or less since this limitation is addressed by the teachings of Laus et al. However, the examiner puts on the record that Schacht et al. indeed teach nanoparticles having size less than 500 nm. Schact et al. teach in general, hydrophilic polymer-shielded and/or bioactive agent modified DNA-containing polyelectrolyte complexes constructed in accordance with this invention will be particles having dimensions within a monodisperse size range of less than 100 nm in diameter, generally less than 70 nm in diameter, and possibly approaching an ideal size of 30-40 nm diameter (column 8, lines 12-18). *Applicants also argue that Laus uses soft shell for a completely different purpose than Schacht. In Schacht the active ingredient is in the core and the shell is used as a protective coating. In Laus the active ingredient is attached to*

the shell, which is used as a means of anchoring the active ingredient to the core. In view of the different roles played by the core and shell in each of Laus and Schacht the skilled person would not have been motivated to combine these documents. Therefore, claim 4 is non-obvious over Laus in view of Schacht. The assertions applicants set forth above are unpersuasive because the features the examiner solely used Schacht et al. to demonstrate that the polymers recited in instant claim 4 are clearly known to be used in nanoparticles based delivery systems. The skilled artisan would have been motivated to use polymers with reactive alkyl amino functional groups (which would include those monomers found in instant claim 4) since they are taught by Schacht et al. as being suitable for bonding and forming a protective coating or shield (abstract and column 19, lines 22-25). Furthermore, the way how the nanoparticles are assembled would not be afforded any weight because applicants are not claiming a method of making these assemblies rather a product. Applicants have not demonstrated how their product is patentably distinct from the cited prior arts nor do the claims as currently written distinguish the instant invention over the prior arts. In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 6 are rejected 35 U.S.C. 103(a) as being unpatentable over Laus et al. (Journal of Controlled Release 2001, 72, 225-309) in view of Jon et al. (Langmuir, 19, 9989-9993, 2003).

Applicant Claims

The limitations of instant claim 1 are set forth above. Instant claim 6 further specifies the monomers used to form the nanoparticles.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Laus et al. are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Laus et al. do not teach the specific monomers recited in the instant claims. This deficiency is cured by Schacht et al.

Jon et al. teach nonbiofouling polymeric self-assembled monolayers (title). One of the **antifouling polymers comprises polyethylene glycol methyl ether methacrylate** (page 9990). **The polymer coating reduces the absorption of nonspecific polymer** (figure 2, page 9992).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary in the art at the time the invention was made to incorporate polyethylene glycol methyl ether methacrylate for use as a coating since it is taught as a suitable polymer for creating nonfouling surfaces by Jon et al. The skilled artisan would have been motivated to incorporate polyethylene

glycol methyl ether methacrylate monomers to control the amount of protein immobilized on the microspheres. Additionally, the antifouling properties of the polyethylene glycol would prevent the adsorption of unwanted biopolymers upon administration of the microsphere to a subject. The skilled artisan would have a reasonable expectation of success at incorporating the polyethylene glycol methyl ether methacrylate since Laus et al. already teaches the use of copolymers comprising methacrylate.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Response to arguments

Applicants' arguments filed 11/25/09 have been fully considered but they are not persuasive. *Applicants argue that Jon is concerned with devices and hardware therefore the skilled person would not have been motivated to combine this teaching of Jon concerning medical devices with the teaching of Laus, which relates to microspheres as a protein delivery system. Furthermore, Jon does not teach nanoparticles with an average diameter of less than 500 nm. Therefore, Jon in combination of Laus does not render amended claim 1 obvious. As claim 6 depends from claim 1, the rejection of claim 6 for obviousness can be withdrawn.* The limitations of instant claim 1 are clearly rendered obvious and applicants' arguments regarding instant claim 1 are rebutted as set forth above. Since those rebuttal arguments also apply in this section of the rejection the examiner incorporates the rebuttal arguments by reference in this section too. Furthermore, the examiner contends that one of ordinary skill in the art would have been motivated to combine the teachings of Laus et al. and Jon et al. because both references

teach the use of polymers to improve surfaces for the non-specific adsorption of proteins. This same purpose of the polymers will apply in numerous applications including microspheres, biomaterials used for implants and tissue engineering etc. Applicants have not demonstrated how their product is patentably distinct from the cited prior arts nor do the claims as currently written distinguish the instant invention over the prior arts. In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 8 are rejected 35 U.S.C. 103(a) as being unpatentable over Laus et al. (Journal of Controlled Release 2001, 72, 225-309) in view of Melker et al. (US Patent No. 6974706) .

Applicant Claims

The limitations of instant claim 1 are set forth above. Instant claim 8 further specifies the nanoparticles further comprise a fluorescent chromophore.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Laus et al. are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Laus et al. do not teach the incorporation of a fluorescent chromophore. This deficiency is cured by Melker et al.

Melker et al. teach nanotechnology, in particular nanoparticles, offers many advantages when used for applications such as the delivery of bioactive agents (i.e., DNA, AIDS drugs, gene therapy, immunosuppressants, chemotherapeutics), and drug uptake and degradation (i.e., enzyme encapsulation). For example, **nanoparticles have been proposed as providing site-specific distribution of drugs to, and minimization of loss from, a target site**. Appropriately sized particles have been proposed wherein such particles can be delivered to selected tissues to release their drug load in a controlled and sustained manner (column 1, lines 32-42). Melker et al. teach a unique method for diagnosing a condition and/or disease in a patient by utilizing a nanoparticle-based biosensor that includes nanoparticles, aptamers, and volatile or "surrogate" biomarkers. Melker et al. teach the incorporation of the so called molecular beacons such as chromophores to provide a means for signaling and quantifying detected target analytes/biomarkers in exhaled breath (column 6, lines 35-38).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary in the art at the time the invention was made to incorporate fluorescent chromophore in nanoparticulate based systems because Melker et al. teach the incorporation of chromophores in nanoparticles. The skilled artisan would have been motivated to incorporate fluorescent chromophore to provide a means for signaling and quantifying detected target analytes/biomarkers

(column 6, lines 35-38). The skilled artisan would have a reasonable expectation of success at incorporating fluorescent chromophore since Melker et al. already teaches the use of chromophores for detection in similar nanoparticulate systems.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicants' arguments filed 11/25/09 have been fully considered but they are not persuasive. *Applicants argue that Melker are directed to a method for detecting biological conditions through non- invasive analysis of bodily fluid samples, including exhaled breath and blood. Melker is quite clear that it is an essential feature of their method that it is non-invasive. In contrast, Laus describes use of their microspheres as "protein delivery systems." There is no motivation for the skilled person to try to apply the teachings of Melker concerning a non-invasive method to the microspheres of Laus.* The examiner respectfully disagrees with applicants' assertion because one of ordinary skill in the art would have been motivated to combine the two references because the skilled artisan recognizes that both Laus et al. and Melker teach nanoparticles based systems. Furthermore, regarding the limitation of instant claim 8 the skilled artisan would have been motivated to incorporate fluorescent chromophore to provide a means for signaling and quantifying detected target analytes/biomarkers (column 6, lines 35-38). Applicants have not demonstrated how their product is patentably distinct from the cited prior arts nor do the claims as currently written distinguish the instant invention over the prior arts. In light of the forgoing discussion, one of ordinary skill in the art would have

concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laus et al. (Journal of Controlled Release 2001, 72, 225-309) in view of Le Buanec et al. (Biomedicine and Pharmacology 2001, 55, 316-320).

Applicant Claims

The limitations of instant claim 1 are set forth above. Instant claim 10 recites the nanoparticle of claim 1 which further comprises a pharmacologically active agent absorbed on the surface. Instant claim 11 further specifies the agent is a disease associated antigen while claims 12 and 14-15 further specify the type of antigen.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Laus et al. are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Laus et al. do not specifically teach the absorption of a pharmaceutically active agent such as an antigen. This deficiency is cured by Le Buanec et al.

Le Buanec et al. teach **the use of microspheres for the administration of Tat toxoid** (Materials and methods; Immunogen preparation).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary skill in the art at the time of the present invention was made to incorporate HIV Tat toxin in the since Le Buanec et al. teach the use of microparticles for the administration of HIV Tat toxin. The skilled artisan would have been motivated to use the microparticles of Laus et al. for the formation of a vaccine using Tat toxin since Le Buanec et al. teach that Tat toxin is advantageously administered in such a way as to produce a mucosal immune response. The skilled artisan would have had a reasonable expectation of success in incorporating HIV Tat toxin since Laus et al. already teaches that the microparticles are suitable for protein absorption.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicants' arguments filed 11/25/09 have been fully considered but they are not persuasive. *Applicants argue that in Le Buanec the antigen is being encapsulated not adsorbed on the surface of the nanoparticles. There would have been no motivation for the skilled person to have combined the teachings of Le Buanec with those of Laus. Also, the teaching of Le Buanec does not overcome the failure of Laus to disclose or suggest*

nanoparticles with an average diameter of less than 500 nm, as specified in amended claim 1. The examiner respectfully disagrees with these assertions because the specific features of adsorption of the protein and particle size diameters are rendered obvious by the teachings of Laus as set forth above. Furthermore, a careful review of the references cited in Le Buanec reveal that the nanoparticles are complexed with the DNA and encapsulated with polylactide-co-glycolide polymer which is equivalent to a shell. One of ordinary skill in that art would infer that during the complexation of the DNA with chitosan based nanoparticles adsorption of the DNA would necessarily occur on the surfaces of the nanoparticles. Additionally, the inclusion of the encapsulation layer is merely a coating shell not related to the interaction between the nanoparticles and the DNA. Moreover, the skilled artisan would have been motivated to use the microparticles of Laus et al. for the formation of a vaccine using Tat toxin since Le Buanec et al. teach that Tat toxin is advantageously administered in such a way as to produce a mucosal immune response. Applicants have not demonstrated how their product is patentably distinct from the cited prior arts nor do the claims as currently written distinguish the instant invention over the prior arts. In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Claims 1-8 and 10-15 are rejected. Claims 9 and 16-20 are withdrawn. Claims 21-23 are cancelled. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIGABU KASSA whose telephone number is (571)270-5867. The examiner can normally be reached on 9 am-5 pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne P. Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tigabu Kassa 02/19/10

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619